(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 June 2005 (09.06.2005)

PCT

(10) International Publication Number
WO 2005/051922 A1

(51) International Patent Classification[7]: C07D 239/90, 401/06, A61K 31/505, A61P 35/00

(21) International Application Number: PCT/US2004/039448

(22) International Filing Date: 24 November 2004 (24.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/525,059 25 November 2003 (25.11.2003) US

(71) Applicant *(for all designated States except US)*: **CHIRON CORPORATION** [US/US]; Intellectual Property Department R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WANG, Weibo** [US/US]; Intellectual Property Department R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US). **LAGNITON, Liana, M.** [AU/US]; Intellectual Property Department R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US). **CONSTANTINE, Ryan, N.** [US/US]; Intellectual Property Department R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US). **DESAI, Manoj, C.** [US/US]; Intellectual Property Department R440, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(74) Agent: **RENZONI, George, E.**; Christensen, O'Connor, Johnson & Kindness PLLC, 1420 Fifth Avenue, Suite 2800, Seattle, WA 98101-2347 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

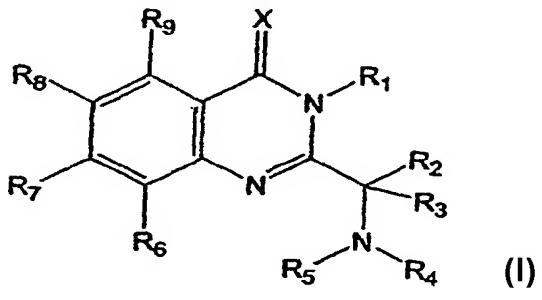
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/051922 A1

(54) Title: QUINAZOLINONE COMPOUNDS AS ANTICANCER AGENTS



(I)

(57) Abstract: Quinazolinone compounds, pharmaceutically acceptable salts, and prodrugs thereof; compositions that include a pharmaceutically acceptable carrier and one or more of the quinazolinone compounds, either alone or in combination with at least one additional therapeutic agent. Methods of using the quinazolinone compounds, either alone or in combination with at least one additional therapeutic agent as KSP inhibitors, in the prophylaxis or treatment of proliferative diseases.

QUINAZOLINONE COMPOUNDS AS ANTICANCER AGENTS

FIELD OF THE INVENTION

The present invention relates to new quinazolinone compounds, their pharmaceutically acceptable salts, and prodrugs thereof; compositions of the new compounds, either alone or in combination with at least one additional therapeutic agent, with a pharmaceutically acceptable carrier; and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of proliferative diseases.

BACKGROUND OF THE INVENTION

Kinesins are motor proteins that use adenosine triphosphate to bind to microtubules and generate mechanical force. Kinesins are characterized by a motor domain having about 350 amino acid residues. The crystal structures of several kinesin motor domains have been resolved.

Currently, about one hundred kinesin-related proteins (KRP) have been identified. Kinesins are involved in a variety of cell biological processes including transport of organelles and vesicles, and maintenance of the endoplasmatic reticulum. Several KRPs interact with the microtubules of the mitotic spindle or with the chromosomes directly, and appear to play a pivotal role during the mitotic stages of the cell cycle. These mitotic KRPs are of particular interest for the development of cancer therapeutics.

Kinesin spindle protein (KSP) (also known as Eg5, HsEg5, KNSL1, or KIFII) is one of several kinesin-like motor proteins that are localized to the mitotic spindle and known to be required for formation and/or function of the bipolar mitotic spindle.

In 1995, the depletion of KSP using an antibody directed against the C-terminus of KSP was shown to arrest HeLa cells in mitosis with monoastral microtubule arrays (Blangy et al., *Cell 83*:1159-1169, 1995). Mutations in bimC and cut7 genes, which are considered to be homologues of KSP, cause failure in centrosome separation in Aspergillus nidulans (Enos, A.P., and N.R. Morris, *Cell 60*:1019-1027, 1990) and Schizosaccharomyces pombe (Hagan, I., and M. Yanagida, *Nature 347*:563-566, 1990). Treatment of cells with either ATRA (all trans-retinoic acid), which reduces KSP expression on protein level, or depletion of KSP using antisense oligonucleotides

revealed a significant growth inhibition in DAN-G pancreatic carcinoma cells indicating that KSP might be involved in the antiproliferative action of all trans-retinoic acid (Kaiser, A., et al., *J. Biol. Chem. 274*, 18925-18931, 1999). Interestingly, the Xenopus laevis Aurora-related protein kinase pEg2 was shown to associate and phosphorylate XlEg5 (Giet, R., et al., *J. Biol. Chem. 274*:15005-15013, 1999). Potential substrates of Aurora-related kinases are of particular interest for cancer drug development. For example, Aurora 1 and 2 kinases are overexpressed on protein and RNA level and the genes are amplified in colon cancer patients.

The first cell permeable small molecule inhibitor for KSP, "monastrol," was shown to arrest cells with monopolar spindles without affecting microtubule polymerization as do conventional chemotherapeutics such as taxanes and vinca alkaloids (Mayer, T.U., et al., *Science 286*:971-974, 1999). Monastrol was identified as an inhibitor in phenotype-based screens and it was suggested that this compound may serve as a lead for the development of anticancer drugs. The inhibition was determined not to be competitive in respect to adenosine triphosphate and to be rapidly reversible (DeBonis, S., et al., *Biochemistry 42*:338-349, 2003; Kapoor, T.M., et al., *J. Cell Biol. 150*:975-988, 2000).

Recently, other KSP kinesin inhibitors have been described. WO 02/057244 and WO 02/056880 describe phenothiazine compounds and triphenylmethane compounds, respectively, for treating proliferative diseases. WO 02/078639 describes cyano-substituted dihydropyrimidine compounds for treating proliferative diseases. U.S. Patent No. 6,472,521 describes oligonucleotides and oligonucleotide derivatives for inhibiting human KSP expression.

WO 01/98278, WO 01/30768, and WO 03/039460 describe quinazolinone compounds that are useful in treating cellular proliferative diseases associated with KSP activity. The compounds described in these references are 2-(2-aminomethyl)quinazolinone derivatives. The quinazolinone compounds described in WO 01/98278 and WO 01/30768 have 2-aminomethyl substituents that are either amine, amide, or sulfonamide substituents. The quinazolinone compounds described in WO 03/039460 have the amino group of the 2-aminomethyl substituent incorporated into a 5-12 membered nitrogen-containing heterocycle.

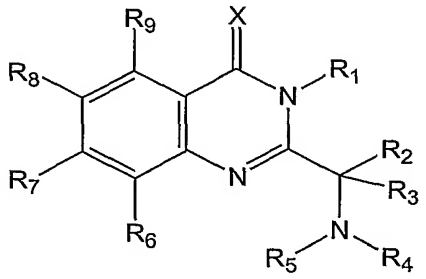
WO 03/050064 describes thienopyrimidinone compounds that are useful for treating cellular proliferative disease, for treating disorders associated with KSP activity, and for inhibiting KSP.

WO 03/103575 describes heterocyclic-fused pyrimidinone derivatives that are inhibitors of the mitotic KSP and that are useful in the treatment of cellular proliferative diseases. These derivatives are N-heterocyclic-fused pyrimidinone derivatives. Representative derivatives that are described include pyrido[α,β-γ]pyrimidin-δ-ones, pyrimido[α,β-γ]pyrimidin-δ-ones, pyrimido[α,β-γ]pyridazin-δ-ones, and pteridin-4-ones.

SUMMARY OF THE INVENTION

In one aspect of the present invention, new quinazolinone compounds, their pharmaceutically acceptable salts, and prodrugs thereof are provided. The quinazolinone compounds, pharmaceutically acceptable salts, and prodrugs are KSP inhibitors and are useful in the treating cellular proliferation diseases.

In one embodiment, the quinazolinone compounds have the formula (I):



I

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

X is O or S;

R_1 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl,

(7) substituted or unsubstituted heterocyclyl,

(8) substituted or unsubstituted alkylsulfonyl, and

(9) substituted or unsubstituted arylsulfonyl;

R_2 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl, and

(4) substituted or unsubstituted alkynyl;

R_3 is selected from the group consisting of

(1) CO_2R_{10},

(2) COR_{10},

(3) $CONR_{11}R_{12}$,

(4) $S(O)_mR_{13}$, and

(5) $SO_2NR_{14}R_{15}$; or

R_2 and R_3 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic or heterocyclic ring;

with the proviso that when R_4 and R_5 are taken together to form a 5- to 12-membered heterocyclic ring, R_3 is $CONR_{11}R_{12}$ or R_2 and R_3 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic or heterocyclic ring;

R_4 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl, and

(7) substituted or unsubstituted heterocyclyl;

R_5 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkoxy,

(4) substituted or unsubstituted aryl,

(5) substituted or unsubstituted heteroaryl,

(6) substituted or unsubstituted heterocyclyl,

(7) COR_{17},

(8) CO_2R_{18},

(9) $CONR_{19}R_{20}$, and

(10) SO_2R_{21}; or

R_4 and R_5 are taken together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclyl ring, wherein the heteroaryl ring contains one or two ring heteroatoms, wherein the heterocyclyl ring contains one or two ring heteroatoms, and wherein the heteroaryl or heterocyclyl ring is optionally substituted with a halogen, alkyl, hydroxy, amino, cyano, alkylamino, dialkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, aryl, aryloxy, heteroaryl, arylalkyl, heterocycle, aminocarbonyl, carbonylamino, alkylcarbonyl, alkylcarboxy, alkylaminocarbonyl, alkylcarbonylamino, carbocycle, or heteroarylalkyl group; with the proviso that when R_4 and R_5 taken together with the nitrogen atom to which they are attached form a 5-membered heterocyclic ring, the heterocyclic ring is not a 2,4-dioxo-3-oxazolidinyl ring, a 2,5-dioxo-1-imidazolidinyl ring, or a 2,4,5-trioxo-1-imidazolidinyl ring;

R_6, R_7, R_8, and R_9 are independently selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) amino,

(6) cyano,

(7) alkoxy,

(8) alkylthio,

(9) methylenedioxy,

(10) haloalkoxy,

(11) CO_2R_{10},

(12) COR_{10},

(13) OR_{10},

(14) $CONR_{11}R_{12}$,

(15) substituted or unsubstituted alkyl,

(16) substituted or unsubstituted aryl,

(17) substituted or unsubstituted heteroaryl,

(18) substituted or unsubstituted alkylamino,

(19) substituted or unsubstituted dialkylamino,

(20) substituted or unsubstituted alkylsulfonyl,

(21) substituted or unsubstituted arylsulfonyl,

(22) substituted or unsubstituted alkylcarboxy,

(23) substituted or unsubstituted carboxamido,

(24) substituted or unsubstituted carboxyamino,

(25) substituted or unsubstituted aminocarboxy,

(26) substituted or unsubstituted aminocarbonyl, and

(27) substituted or unsubstituted alkylsulfonamido;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl, and

(7) substituted or unsubstituted heterocyclyl; or

R_{11} and R_{12}, R_{14} and R_{15}, or R_{19} and R_{20} taken together form a 3- to 7-membered carbocyclic or heterocyclic ring; and

m = 0, 1, or 2.

In another aspect, the present invention provides methods for treating proliferative diseases in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I) effective to reduce or prevent cellular proliferation in the subject.

In another aspect of the present invention, methods for treating proliferative diseases in a human or animal subject in need of such treatment, comprising administering to said subject an amount of a compound of formula (I) effective to reduce or prevent cellular proliferation in the subject in combination with at least one additional agent for the treatment of cancer.

In other aspects, the present invention provides therapeutic compositions, comprising at least one compound of formula (I) in combination with one or more additional agents for the treatment of cancer, as are commonly employed in cancer therapy.

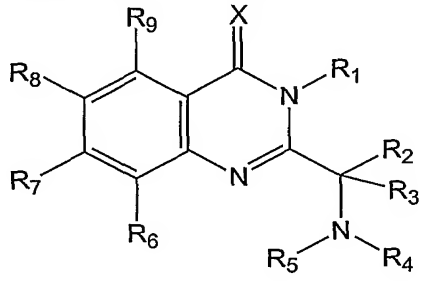
The compounds of the invention are useful in the treatment of cancers, including, for example, lung and bronchus; prostate; breast; pancreas; colon and rectum; thyroid; stomach; liver and intrahepatic bile duct; kidney and renal pelvis; urinary bladder; uterine corpus; uterine cervix; ovary; multiple myeloma; esophagus; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; non-hodgkin lymphoma; melanoma; and villous colon adenoma.

The invention further provides compositions, kits, methods of use, and methods of manufacture as described in the detailed description of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In one aspect of the present invention, new quinazolinone compounds, their pharmaceutically acceptable salts, and prodrugs thereof are provided. The quinazolinone compounds, pharmaceutically acceptable salts, and prodrugs are KSP inhibitors and are useful in the treating cellular proliferation diseases.

The quinazolinone compounds have the formula (I):



I

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

X is O or S;

R_1 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl,

(7) substituted or unsubstituted heterocyclyl,

(8) substituted or unsubstituted alkylsulfonyl, and

(9) substituted or unsubstituted arylsulfonyl;

R_2 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl, and

(4) substituted or unsubstituted alkynyl;

R_3 is selected from the group consisting of

(1) CO_2R_{10},

(2) COR_{10},

(3) $CONR_{11}R_{12}$,

(4) $S(O)_mR_{13}$, and

(5) $SO_2NR_{14}R_{15}$; or

R_2 and R_3 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic or heterocyclic ring;

with the proviso that when R_4 and R_5 are taken together to form a 5- to 12-membered heterocyclic ring, R_3 is $CONR_{11}R_{12}$ or R_2 and R_3 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic or heterocyclic ring;

R_4 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl, and

(7) substituted or unsubstituted heterocyclyl;

R_5 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkoxy,

(4) substituted or unsubstituted aryl,

(5) substituted or unsubstituted heteroaryl,

(6) substituted or unsubstituted heterocyclyl,

(7) COR_{17},

(8) CO_2R_{18},

(9) $CONR_{19}R_{20}$, and

(10) SO_2R_{21}; or

R_4 and R_5 are taken together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclyl ring, wherein the heteroaryl ring contains one or two ring heteroatoms, wherein the heterocyclyl ring contains one or two ring heteroatoms, and wherein the heteroaryl or heterocyclyl ring is optionally substituted with a halogen, alkyl, hydroxy, amino, cyano, alkylamino, dialkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, aryl, aryloxy, heteroaryl, arylalkyl, heterocycle, aminocarbonyl, carbonylamino, alkylcarbonyl, alkylcarboxy, alkylaminocarbonyl, alkylcarbonylamino, carbocycle, or heteroarylalkyl group; with the proviso that when R_4 and R_5 taken together with the nitrogen atom to which they are attached form a 5-membered heterocyclic ring, the heterocyclic ring is not a 2,4-dioxo-3-oxazolidinyl ring, a 2,5-dioxo-1-imidazolidinyl ring, or a 2,4,5-trioxo-1-imidazolidinyl ring;

R_6, R_7, R_8, and R_9 are independently selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) hydroxy,

(4) nitro,

(5) amino,

(6) cyano,

(7) alkoxy,

(8) alkylthio,

(9) methylenedioxy,

(10) haloalkoxy,

(11) CO_2R_{10},

(12) COR_{10},

(13) OR_{10},

(14) $CONR_{11}R_{12}$,

(15) substituted or unsubstituted alkyl,

(16) substituted or unsubstituted aryl,

(17) substituted or unsubstituted heteroaryl,

(18) substituted or unsubstituted alkylamino,

(19) substituted or unsubstituted dialkylamino,

(20) substituted or unsubstituted alkylsulfonyl,

(21) substituted or unsubstituted arylsulfonyl,

(22) substituted or unsubstituted alkylcarboxy,

(23) substituted or unsubstituted carboxamido,

(24) substituted or unsubstituted carboxyamino,

(25) substituted or unsubstituted aminocarboxy,

(26) substituted or unsubstituted aminocarbonyl, and

(27) substituted or unsubstituted alkylsulfonamido;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl, and

(7) substituted or unsubstituted heterocyclyl; or

R_{11} and R_{12}, R_{14} and R_{15}, or R_{19} and R_{20} taken together form a 3- to 7-membered carbocyclic or heterocyclic ring; and

m = 0, 1, or 2.

In one embodiment, X is O.

In one embodiment, R_1 is arylalkyl. In one embodiment, the arylalkyl is benzyl or substituted benzyl. In one embodiment, R_1 is a halo-substituted benzyl. In one embodiment, R_1 is 3-chlorobenzyl. In one embodiment, R_1 is 3-fluorobenzyl. In one embodiment, R_1 is 3-methoxybenzyl. In one embodiment, R_1 is 3-trifluoromethylbenzyl.

In one embodiment, R_1 is 3-trifluoromethoxybenzyl. In one embodiment, R_1 is 3,5-dimethylbenzyl. In one embodiment, R_1 is 2-naphthylmethyl.

In one embodiment, R_2 is hydrogen and R_3 is CO_2R_{10}. In one embodiment, R_{10} is alkyl.

In one embodiment, R_2 is hydrogen and R_3 is $CONR_{11}R_{12}$. In one embodiment, R_{11} and R_{12} are alkyl. In one embodiment, R_{11} and R_{12} are methyl. In one embodiment, R_{11} and R_{12} are taken together to with the nitrogen atom to which they are attached from a 3- to 7-membered heterocyclic ring.

In one embodiment, R_4 is amino-substituted alkyl. In one embodiment, R_4 is 3-aminopropyl.

In one embodiment, R_5 is hydrogen, alkyl, aryl, or COR_{17}. In one embodiment, R_{17} is aryl, arylalkyl, alkyl-substituted aryl, or halogen-substituted aryl.

In one embodiment, R_6, R_8, and R_9 are hydrogen.

In one embodiment, R_7 is a halogen.

For the compounds of formula (I), representative substituted alkyl groups include arylalkyl, heteroarylalkyl, heterocyclyalkyl, aminoalkyl, alkylaminoalkyl, dialkyaminoalkyl, and sulfonamidoalkyl groups. Representative substituted aryl groups include sulfonamidoaryl groups. Representative substituted heteroaryl groups include alkylheteroaryl groups.

In other aspects, the present invention provides methods for manufacture of compounds of formula (I). Methods of making representative compounds of the invention are described in Examples 1 and 2. It is further contemplated that, in addition to the compounds of formula (I), intermediates and their corresponding methods of syntheses are included within the scope of the invention. Representative compounds of the invention are illustrated in Table 1 in Example 3.

In other aspects, the present invention provides compositions that include the KSP inhibitors described herein, and methods that utilize the KSP inhibitors described herein.

In one aspect, the present invention provides pharmaceutical compositions comprising at least one quinazolinone compound (e.g., a compound of formula (I)) together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

A number of suitable anticancer agents to be used as combination therapeutics are contemplated for use in the compositions and methods of the present invention. Suitable

anticancer agents to be used in combination with the compounds of the invention include agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g., interferons [e.g., IFN-a] and interleukins [e.g., IL-2]); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for coadministration with the disclosed compounds of formula (I) are known to those skilled in the art.

In certain embodiments, anticancer agents to be used in combination with compounds of the present invention comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation; kinase inhibitors (e.g., Epidermal Growth Factor Receptor [EGFR] kinase inhibitor, Vascular Growth Factor Receptor [VGFR] kinase inhibitor, Fibroblast Growth Factor Receptor [FGFR] kinase inhibitor, Platelet-derived Growth Factor Receptor [PGFR] I kinase inhibitor, and Bcr-Abl kinase inhibitors such as STI-571, Gleevec, and Glivec]); antisense molecules; antibodies [e.g., Herceptin and Rituxan]; anti-estrogens [e.g., raloxifene and tamoxifen]; anti-androgens [e.g., flutamide, bicalutamide, finasteride, amino-glutethamide, ketoconazole, and corticosteroids]; cyclooxygenase 2 (COX-2) inhibitors [e.g., Celecoxib, meloxicam, NS-398, and non-steroidal anti-inflammatory drugs (NSAIDs)]; and cancer chemotherapeutic drugs [e.g., irinotecan (Camptosar), CPT-11, fludarabine (Fludara), dacarbazine (DTIC), dexamethasone, mitoxantrone, Mylotarg, VP-16, cisplatinum, 5-FU, Doxrubicin, TAXOTERE or TAXOL]; cellular signaling molecules; ceramides and cytokines; and staurosprine; and the like.

In other aspects, the invention provides methods for using the compounds described herein. For example, the compounds described herein can be used in the treatment of cancer. The compounds described herein can also be used in the manufacture of a medicament for the treatment of cancer.

In one embodiment, the present invention provides methods of treating human or animal subjects suffering from a cellular proliferative disease, such as cancer. The present invention provides methods of treating a human or animal subject in need of such

treatment, comprising administering to the subject a therapeutically effective amount of an quinazolinone compound (e.g., a compound of formula (I)), either alone or in combination with other anticancer agents.

In another embodiment, the present invention provides methods for treating a cellular proliferative disease in a human or animal subject in need of such treatment comprising, administering to said subject an amount of an quinazolinone compound (e.g., a compound of formula (I)) effective to reduce or prevent cellular proliferation or tumor growth in the subject.

In another embodiment, the present invention provides methods for treating a cellular proliferative disease in a human or animal subject in need of such treatment comprising administering to said subject an amount of an quinazolinone compound (e.g., a compound of formula (I)) effective to reduce or prevent cellular proliferation in the subject in combination with at least one additional agent for the treatment of cancer.

The present invention provides compounds that are inhibitors of KSP. The inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of KSP is indicated, e.g., in the treatment of cellular proliferative diseases such as tumor and/or cancerous cell growth mediated by KSP. In particular, the compounds are useful in the treatment of human or animal (e.g., murine) cancers, including, for example, lung and bronchus; prostate; breast; pancreas; colon and rectum; thyroid; stomach; liver and intrahepatic bile duct; kidney and renal pelvis; urinary bladder; uterine corpus; uterine cervix; ovary; multiple myeloma; esophagus; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; non-hodgkin lymphoma; melanoma; and villous colon adenoma.

In another embodiment, the invention provides methods of treating an KSP mediated disorder. In one method, an effective amount of an quinazolinone compound is administered to a patient (e.g., a human or animal subject) in need thereof to mediate (or modulate) KSP activity.

A representative assay for determining KSP inhibitory activity is described in Example 4.

The following definitions are provided to better understand the invention.

As used herein, the term "quinazolinone" refers to a quinazolinone compound having a carbonyl or thiocarbonyl group at position 4.

"Alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)-CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2-CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus the phrase "alkyl groups" includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 12 carbon atoms.

"Alkylene" refers to the same residues as noted above for "alkyl," but having two points of attachment. Exemplary alkylene groups include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$), and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})-$).

"Alkenyl" refers to straight chain, branched, or cyclic radicals having one or more carbon-carbon double bonds and from 2 to about 20 carbon atoms. Preferred alkenyl groups include straight chain and branched alkenyl groups and cyclic alkenyl groups having 2 to 12 carbon atoms.

"Alkynyl" refers to straight chain, branched, or cyclic radicals having one or more carbon-carbon triple bonds and from 2 to about 20 carbon atoms. Preferred alkynyl groups include straight chain and branched alkynyl groups having 2 to 12 carbon atoms.

Alkyl, alkenyl, and alkynyl groups may be substituted. "Substituted alkyl" refers to an alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl

groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups further include alkyl groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heteroaryl, heterocyclyl, or cycloalkyl group. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluoro, chloro, or bromo group. Another preferred substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other preferred substituted alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, or aryloxy group. Other preferred substituted alkyl groups include alkyl groups that have an amine, or a substituted or unsubstituted alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclylamine, diheterocyclylamine, (alkyl)(heterocyclyl)amine, or (aryl)(heterocyclyl)amine group. Still other preferred substituted alkyl groups include those in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heteroaryl, heterocyclyl, or cycloalkyl group. Examples of substituted alkyl are: $-(CH_2)_3NH_2$, $-(CH_2)_3NH(CH_3)$, $-(CH_2)_3NH(CH_3)_2$, $-CH_2C(=CH_2)CH_2NH_2$, $.CH_2C(=O)CH_2NH_2$, $-CH_2S(=O)_2CH_3$, $-CH_2OCH_2NH_2$, $-CO_2H$. Examples of substituents of substituted alkyl are: $-CH_3$, $-C_2H_5$, $-CH_2OH$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-OCF_3$, $-OC(=O)CH_3$, $-OC(=O)NH_2$, $-OC(=O)N(CH_3)_2$, $-CN$, $-NO_2$, $-C(=O)CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-NH_2$, $-N(CH_3)_2$, $-NHSO_2CH_3$, $-NHCOCH_3$, $-NHC(=O)OCH_3$, $-NHSO-_2CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, Halo.

"Substituted alkenyl" has the same meaning with respect to alkenyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the

non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon.

"Substituted alkynyl" has the same meaning with respect to alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

"Alkoxy" refers to RO- wherein R is alkyl. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, trifluoromethoxy, and the like.

"Halogen" or "halo" refers to chloro, bromo, fluoro, and iodo groups. The term "haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms. The term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms.

"Amino" refers herein to the group $-NH_2$. The term "alkylamino" refers herein to the group –NRR' where R is alkyl and R' is hydrogen or alkyl. The term "arylamino" refers herein to the group –NRR' where R is aryl and R' is hydrogen, alkyl, or aryl. The term "aralkylamino" refers herein to the group –NRR' where R is aralkyl and R' is hydrogen, alkyl, aryl, or aralkyl.

"Alkoxyalkyl" refers to the group $-alk_1-O-alk_2$ where alk_1 is alkyl or alkenyl, and alk_2 is alkyl or alkenyl. The term "aryloxyalkyl" refers to the group -alkyl O-aryl. The term "aralkoxyalkyl" refers to the group -alkylenyl-O-aralkyl.

"Alkoxyalkylamino" refers herein to the group –NR-(alkoxyalkyl), where R is typically hydrogen, aralkyl, or alkyl.

"Aminocarbonyl" refers herein to the group $-C(O)-NH_2$. "Substituted aminocarbonyl" refers herein to the group –C(O)-NRR' where R is alkyl and R' is hydrogen or alkyl. The term "arylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is aryl and R' is hydrogen, alkyl or aryl. "Aralkylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is aralkyl and R' is hydrogen, alkyl, aryl, or aralkyl.

"Aminosulfonyl" refers herein to the group $-S(O)_2-NH_2$. "Substituted aminosulfonyl" refers herein to the group $-S(O)_2-NRR'$ where R is alkyl and R' is hydrogen or alkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group -aryl-$S(O)_2$–NH-aralkyl.

"Carbonyl" refers to the divalent group –C(O)-.

"Carbonyloxy" refers generally to the group –C(O)-O. Such groups include esters, -C(O)-O-R, where R is alkyl, cycloalkyl, aryl, or aralkyl. The term "carbonyloxycycloalkyl" refers generally herein to both a "carbonyloxycarbocycloalkyl" and a "carbonyloxyheterocycloalkyl," i.e., where R is a carbocycloalkyl or heterocycloalkyl, respectively. The term "arylcarbonyloxy" refers herein to the group -C(O)-O-aryl, where aryl is a mono- or polycyclic, carbocycloaryl or heterocycloaryl. The term "aralkylcarbonyloxy" refers herein to the group –C(O)-O-aralkyl.

"Sulfonyl" refers herein to the group $-SO_2-$. "Alkylsulfonyl" refers to a substituted sulfonyl of the structure $-SO_2R-$ in which R is alkyl. Alkylsulfonyl groups employed in compounds of the present invention are typically alkylsulfonyl groups having from 1 to 6 carbon atoms in its backbone structure. Thus, typical alkylsulfonyl groups employed in compounds of the present invention include, for example, methylsulfonyl (i.e., where R is methyl), ethylsulfonyl (i.e., where R is ethyl), propylsulfonyl (i.e., where R is propyl), and the like. The term "arylsulfonyl" refers herein to the group $-SO_2$-aryl. The term "aralkylsulfonyl" refers herein to the group $-SO_2$-aralkyl. The term "sulfonamido" refers herein to $-SO_2NH_2$.

"Carbonylamino" refers to the divalent group -NH-C(O)- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced alkyl, aryl, or aralkyl group. Such groups include moieties such as carbamate esters (-NH-C(O)-O-R) and amides –NH-C(O)-R, where R is a straight or branched chain alkyl, cycloalkyl, or aryl or aralkyl. The term "alkylcarbonylamino" refers to alkylcarbonylamino where R is alkyl having from 1 to about 6 carbon atoms in its backbone structure. The term "arylcarbonylamino" refers to group –NH-C(O)-R where R is an aryl. Similarly, the term "aralkylcarbonylamino " refers to carbonylamino where R is aralkyl.

"Guanidino" or "guanidyl" refers to moieties derived from guanidine, H_2N-C(=NH)-NH_2. Such moieties include those bonded at the nitrogen atom carrying the formal double bond (the "2"-position of the guanidine, e.g., diaminomethyleneamino, $(H_2N)_2C$=NH-)) and those bonded at either of the nitrogen atoms carrying a formal single bond (the "1-" and/or "3"-positions of the guandine, e.g., H_2N-C(=NH)-NH-)). The hydrogen atoms at any of the nitrogens can be replaced with a suitable substituent, such as alkyl, aryl, or aralkyl.

"Amidino" refers to the moieties R-C(=N)-NR'- (the radical being at the "N^1" nitrogen) and R(NR')C=N- (the radical being at the "N^2" nitrogen), where R and R' can be hydrogen, alkyl, aryl, or aralkyl.

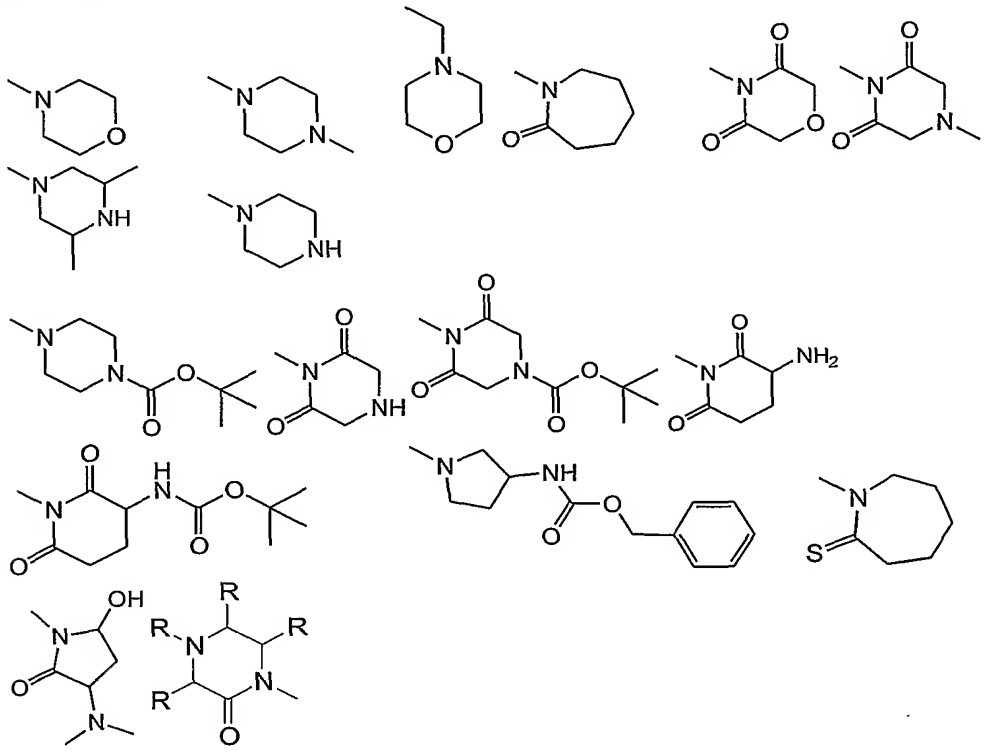
"Cycloalkyl" refers to a mono- or polycyclic, heterocyclic or carbocyclic alkyl substituent. Typical cycloalkyl substituents have from 3 to 8 backbone (i.e., ring) atoms in which each backbone atom is either carbon or a heteroatom. The term "heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 4 heteroatoms in the ring structure. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen, and sulfur. Representative heterocycloalkyl moieties include, for example, morpholino, piperazinyl, piperadinyl, and the like. Carbocycloalkyl groups are cycloalkyl groups in which all ring atoms are carbon. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures.

"Substituted heterocycle," "heterocyclic group," "heterocycle," or "heterocyclyl," as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms maybe optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring independently defined above. The term "heterocycle" thus includes rings in which nitrogen is the heteroatom as well as partially and fully-saturated rings. Preferred heterocycles include, for example: diazapinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazoyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, N-methyl piper-azinyl, azetidinyl, N-methylazetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl, and benzothienyl.

Heterocyclic moieties can be unsubstituted or monosubstituted or disubstituted with various substituents independently selected from hydroxy, halo, oxo (C=O),

alkylimino (RN=, wherein R is alkyl or alkoxy group), amino, alkylamino, dialkylamino, acylaminoalkyl, alkoxy, thioalkoxy, polyalkoxy, alkyl, cycloalkyl or haloalkyl.

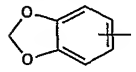
The heterocyclic groups may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



where R is H or a heterocyclic substituent, as described herein.

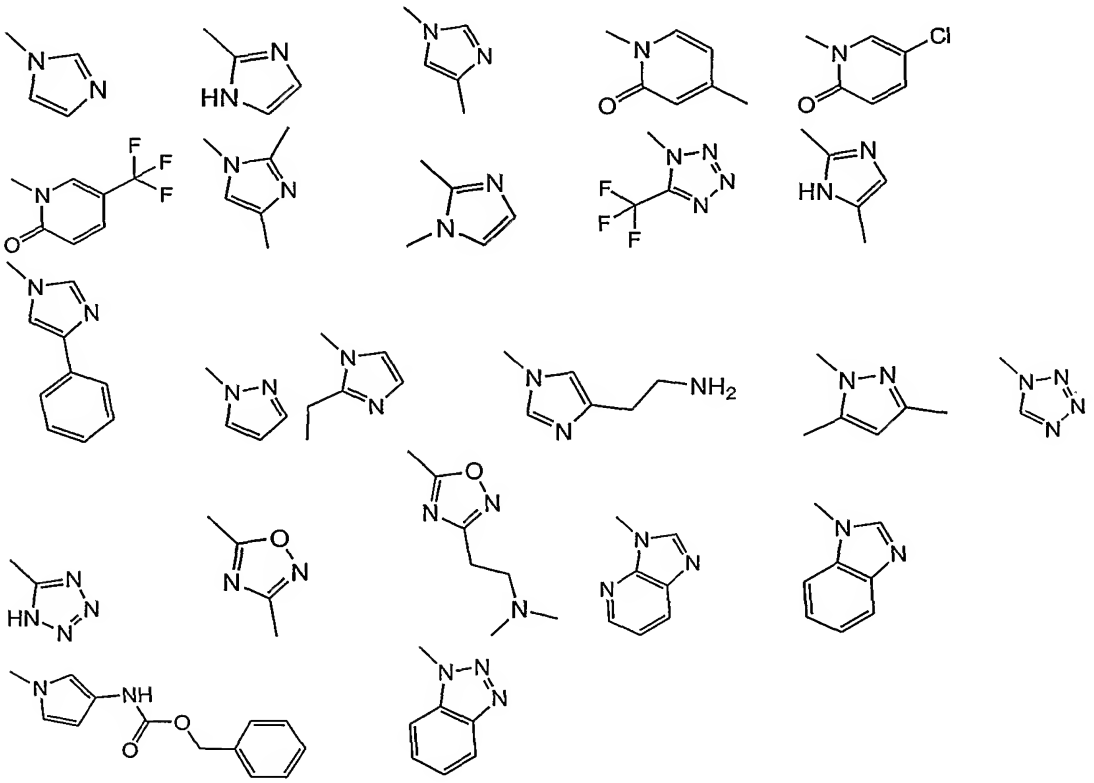
Representative heterocyclics include, for example, imidazolyl, pyridyl, piperazinyl, azetidinyl, thiazolyl, furanyl, triazolyl benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, indolyl, naphthpyridinyl, indazolyl, and quinolizinyl.

"Aryl" refers to optionally substituted monocyclic and polycyclic aromatic groups having from 3 to 14 backbone carbon or hetero atoms, and includes both carbocyclic aryl groups and heterocyclic aryl groups. Carbocyclic aryl groups are aryl groups in which all ring atoms in the aromatic ring are carbon. The term "heteroaryl" refers herein to aryl groups having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms. When used in connection with aryl substituents, the term "polycyclic aryl" refers herein to fused and non-fused cyclic structures in which at least one cyclic structure is aromatic, such as, for example,

benzodioxozolo (which has a heterocyclic structure fused to a phenyl group, i.e.,  , naphthyl, and the like. Exemplary aryl moieties employed as substituents in compounds of the present invention include phenyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like.

"Aralkyl" or "arylalkyl" refers to an alkyl group substituted with an aryl group. Typically, aralkyl groups employed in compounds of the present invention have from 1 to 6 carbon atoms incorporated within the alkyl portion of the aralkyl group. Suitable aralkyl groups employed in compounds of the present invention include, for example, benzyl, picolyl, and the like.

Representative heteroaryl groups include, for example, those shown below. These heteroaryl groups can be further substituted and may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



Representative heteroaryls include, for example, imidazolyl, pyridyl, thiazolyl, triazolyl benzimidazolyl, benzothiazolyl, and benzoxazolyl.

"Biaryl" refers to a group or substituent to which two aryl groups, which are not condensed to each other, are bound. Exemplary biaryl compounds include, for example, phenylbenzene, diphenyldiazene, 4-methylthio-1-phenylbenzene, phenoxybenzene, (2-phenylethynyl)benzene, diphenyl ketone, (4-phenylbuta-1,3-diynyl)benzene, phenylbenzylamine, (phenylmethoxy)benzene, and the like. Preferred optionally substituted biaryl groups include: 2-(phenylamino)-N-[4-(2-phenylethynyl)-phenyl]acetamide, 1,4-diphenylbenzene, N-[4-(2-phenylethynyl)phenyl]-2-[benzyl-amino]-acetamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]propanamide, 2-amino-N-[4-(2-phenyl-ethynyl)phenyl]acetamide, 2-(cyclopropylamino)-N-[4-(2-phenylethynyl)-phenyl]-acetamide, 2-(ethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[(2-methyl-propyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 5-phenyl-2H-benzo-[d]1,3-dioxolene, 2-chloro-1-methoxy-4-phenylbenzene, 2-[(imidazolylmethyl)-amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-phenoxybenzene, N-(2-amino-ethyl)-[4-(2-phenylethynyl)phenyl]carboxamide, 2-{[(4-fluorophenyl)methyl]-amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-{[(4-methylphenyl)methyl]amino}-N-[4-(2-phenyl-ethynyl)phenyl]acetamide, 4-phenyl-1-(trifluoromethyl)benzene, 1-butyl-4-phenyl-benzene, 2-(cyclohexylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethyl-methyl-amino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(butylamino)-N-[4-(2-phenyl-ethynyl)-phenyl]acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(4-pyridylamino)-acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(quinuclidin-3-ylamino)acetamide, N-[4-(2-phenyl-ethynyl)phenyl]pyrrolidin-2-ylcarboxamide, 2-amino-3-methyl-N-[4-(2-phenyl-ethynyl)-phenyl]butanamide, 4-(4-phenylbuta-1,3-diynyl)phenylamine, 2-(dimethyl-amino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)-phenyl]acetamide, 4-ethyl-1-phenylbenzene, 1-[4-(2-phenyl-ethynyl)-phenyl]ethan-1-one, N-(1-carbamoyl-2-hydroxypropyl)[4-(4-phenylbuta-1,3-diynyl)-phenyl]-carbox-amide, N-[4-(2-phenylethynyl)phenyl]propanamide, 4-methoxy-phenyl phenyl ketone, phenyl-N-benzamide, (tert-butoxy)-N-[(4-phenylphenyl)-methyl]-carboxamide, 2-(3-phenyl-phenoxy)ethanehydroxamic acid, 3-phenylphenyl propanoate, 1-(4-ethoxyphenyl)-4-methoxybenzene, and [4-(2-phenylethynyl)phenyl]pyrrole.

"Heteroarylaryl" refers to a biaryl group where one of the aryl groups is a heteroaryl group. Exemplary heteroarylaryl groups include, for example, 2-phenylpyridine, phenylpyrrole, 3-(2-phenylethynyl)pyridine, phenylpyrazole, 5-(2-phenyl-ethynyl)-1,3-dihydropyrimidine-2,4-dione, 4-phenyl-1,2,3-thiadiazole, 2-(2phenyl-ethynyl)pyrazine, 2-phenylthiophene, phenylimidazole, 3-(2-piperazinyl-phenyl)-furan, 3-(2,4-dichlorophenyl)-4-methylpyrrole, and the like. Preferred optionally substituted heteroarylaryl groups include: 5-(2-phenylethynyl)pyrimidine-2-ylamine, 1-methoxy-4-(2-thienyl)benzene, 1-methoxy-3-(2-thienyl)benzene, 5-methyl-2-phenyl-pyridine, 5-methyl-3-phenylisoxazole, 2-[3-(trifluoromethyl)phenyl]furan, 3-fluoro-5-(2-furyl)-2-methoxy-1-prop-2-enylbenzene, (hydroxyimino)(5-phenyl(2-thienyl))-methane, 5-[(4-methylpiperazinyl)methyl]-2-phenylthiophene, 2-(4-ethylphenyl)-thiophene, 4-methyl-thio-1-(2-thienyl)benzene, 2-(3-nitrophenyl)thiophene, (tert-butoxy)-N-[(5-phenyl-(3-pyridyl))methyl]carboxamide, hydroxy-N-[(5-phenyl(3-pyridyl))methyl]-amide, 2-(phenyl-methylthio)pyridine, and benzylimidazole.

"Heteroarylheteroaryl" refers to a biaryl group where both of the aryl groups is a heteroaryl group. Exemplary heteroarylheteroaryl groups include, for example, 3-pyridylimidazole, 2-imidazolylpyrazine, and the like. Preferred optionally substituted heteroarylheteroaryl groups include: 2-(4-piperazinyl-3-pyridyl)furan, diethyl-(3-pyrazin-2-yl(4-pyridyl))amine, and dimethyl{2-[2-(5-methylpyrazin-2-yl)ethynyl](4-pyridyl)}amine.

"Optionally substituted" or "substituted" refers to the replacement of hydrogen with a monovalent or divalent radical. Suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, haloalkyl, alkyamino, haloalkylamino, alkoxy, haloalkoxy, alkoxy-alkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkyl-carbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like.

The substitution group can itself be substituted. The group substituted onto the substitution group can be carboxyl, halo, nitro, amino, cyano, hydroxyl, alkyl, alkoxy, aminocarbonyl, -SR, thioamido, $-SO_3H$, $-SO_2R$, or cycloalkyl, where R is typically hydrogen, hydroxyl or alkyl.

When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at

the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substituents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

"Carboxy-protecting group" refers to a carbonyl group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid function while reactions involving other functional sites of the compound are carried out. In addition, a carboxy protecting group can be attached to a solid support whereby the compound remains connected to the solid support as the carboxylate until cleaved by hydrolytic methods to release the corresponding free acid. Representative carboxy-protecting groups include, for example, alkyl esters, secondary amides and the like.

Certain of the compounds of the invention comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention comprising mixtures of stereoisomers at a particular asymmetrically substituted carbon atom or a single stereoisomer. As a result, racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 "RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY," *Pure Appl. Chem. 45*:13-30, 1976. The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the "Chemical Abstracts Index Guide," Appendix IV, paragraph 203, 1987.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of formula (I). These salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate,

dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemi-sulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-napthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent

compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in Higuchi, T., and V. Stella, "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series 14*, and in "Bioreversible Carriers in Drug Design," in Edward B. Roche (ed.), *American Pharmaceutical Association*, Pergamon Press, 1987, both of which are incorporated herein by reference.

The term "cancer" refers to cancer diseases that can be beneficially treated by the inhibition of KSP, including, for example, solid cancers, such as carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon); myeloid disorders (e.g., myeloid leukemia); and adenomas (e.g., villous colon adenoma). Cancer is a proliferative disease.

The compounds of the invention are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinyl-pyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey, 1991, incorporated herein by reference.

Effective amounts of the compounds of the invention generally include any amount sufficient to detectably inhibit KSP activity by any of the assays described herein, by other KSP activity assays known to those having ordinary skill in the art, or by detecting an inhibition or alleviation of symptoms of cancer.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The compounds of the present invention may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott (ed.), "Methods in Cell Biology," Volume XIV, Academic Press, New York, 1976, p. 33 *et seq.*

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents used in the treatment of cancer. Representative agents useful in combination with the compounds of the invention for the treatment of cancer include, for example, irinotecan, topotecan, gemcitabine, gleevec, herceptin, 5-fluorouracil, leucovorin, carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, trastuzumab, topoisomerase I inhibitors, as well as other cancer chemotherapeutic agents.

The above compounds to be employed in combination with the compounds of the invention will be used in therapeutic amounts as indicated in the *Physicians' Desk Reference* (PDR) 47th Edition (1993), which is incorporated herein by reference, or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

The compounds of the invention and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When

administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

Antiestrogens, such as tamoxifen, inhibit breast cancer growth through induction of cell cycle arrest, that requires the action of the cell cycle inhibitor p27Kip. Recently, it has been shown that activation of the Ras-Raf-MAP Kinase pathway alters the phosphorylation status of p27Kip such that its inhibitory activity in arresting the cell cycle is attenuated, thereby contributing to antiestrogen resistance (Donovan, et al, *J. Biol. Chem. 276*:40888, 2001). As reported by Donovan et al., inhibition of MAPK signaling through treatment with MEK inhibitor changed the phosphorylation status of p27 in hormone refactory breast cancer cell lines and in so doing restored hormone sensitivity. Accordingly, in one aspect, the compounds of formula (I) may be used in the treatment of hormone dependent cancers, such as breast and prostate cancers, to reverse hormone resistance commonly seen in these cancers with conventional anticancer agents.

In hematological cancers, such as chronic myelogenous leukemia (CML), chromosomal translocation is responsible for the constitutively activated BCR-AB1 tyrosine kinase. The afflicted patients are responsive to gleevec, a small molecule tyrosine kinase inhibitor, as a result of inhibition of Ab1 kinase activity. However, many patients with advanced stage disease respond to gleevec initially, but then relapse later due to resistance-conferring mutations in the Ab1 kinase domain. *In vitro* studies have demonstrated that BCR-Av1 employs the Raf kinase pathway to elicit its effects. In addition, inhibiting more than one kinase in the same pathway provides additional protection against resistance-conferring mutations. Accordingly, in another aspect of the invention, the compounds of formula (I) are used in combination with at least one additional agent, such as gleevec, in the treatment of hematological cancers, such as chronic myelogenous leukemia (CML), to reverse or prevent resistance to the at least one additional agent.

In another aspect of the invention, kits that include one or more compounds of the invention are provided. Representative kits include a compound of formula (I) and a package insert or other labeling including directions for treating a cellular proliferative disease by administering an KSP inhibitory amount of the compound.

The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods, which are well known in the art.

The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2690 Separation Module (Milford, MA). The analytical columns were Alltima C-18 reversed phase, 4.6 x 250 mm from Alltech (Deerfield, IL). A gradient elution was used, typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 40 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA). In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

Mass spectrometric analysis was performed on one of two LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; solvent system: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05%TFA; flow rate 0.8 mL/min; molecular weight range 500-1500; cone Voltage 20 V; column temperature 40 °C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; solvent system: 1-95% acetonitrile in water with 0.05%TFA; flow rate 0.4 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30 °C). All masses were reported as those of the protonated parent ions.

GCMS analysis is performed on a Hewlett Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; injector volume: 1 μL; initial column temperature: 50 °C; final column temperature: 250 ° Cramp time: 20 minutes;

gas flow rate: 1 mL/min; column: 5% phenyl methyl siloxane, Model No. HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 300 MHz NMR (Palo Alto, CA). The spectral reference was either TMS or the known chemical shift of the solvent. Some compound samples were run at elevated temperatures (e.g., 75°C) to promote increased sample solubility.

The purity of some of the invention compounds is assessed by elemental analysis (Desert Analytics, Tucson, AZ)

Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

Preparative separations were carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a C-18 reversed phase column. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography were dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous hydroxyamine, and triethyl amine. Typical solvents employed for the reverse phase HPLC were varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

The following are abbreviations used in the examples:

AcOH:	Acetic acid
aq:	Aqueous
ATP:	Adenosine triphosphate
9-BBN	9-Borabicyclo[3.3.1]nonane
Boc:	tert-butoxycarbonyl
Celite	Filter agent
DAP or Dap:	Diaminopropionate
DCM:	Dichloromethane
DEAD:	Diethyl azodicarboxylate
DIEA:	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME:	1,2-Dimethoxyethane
DMF:	N,N-Dimethylformamide
DMSO:	Dimethyl sulfoxide

DPPA:	Diphenyl phosphoryl azide
Et_3N:	Triethylamine
EDC:	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
EDCI:	1-(3-Dimethylaminopropyl)3-ethylcarbodiimide
EtOAc:	Ethyl acetate
EtOH:	Ethanol
Fmoc:	9-Fluorenylmethoxycarbonyl
Gly-OH:	Glycine
HATU:	O-(7-Azabenzotriaazol-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate
HBTU:	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Hex:	Hexane
HOBt:	Butyl alcohol
HOBT:	1-Hydroxybenzotriazole
HPLC:	High pressure liquid chromatography
NIS	N-Iodosuccinimide
IC_{50} value:	The concentration of an inhibitor that causes a 50% reduction in a measured activity.
iPrOH:	Isopropanol
LC/MS:	Liquid chromatography/mass spectrometry
LRMS:	Low resolution mass spectrometry
MeOH:	Methanol
NaOMe:	Sodium methoxide
nm:	Nanometer
NMP:	N-Methylpyrrolidone
PPA	Polyphosphoric acid
PPh_3:	Triphenyl phosphine
PTFE	Polytetrafluoroethylene
RP-HPLC:	Reversed-phase high-pressure liquid chromatography
RT:	Room temperature
sat:	Saturated
TEA:	Triethylamine

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

Thr: Threonine

TLC: Thin layer chromatography

Trt-Br: Tert-butyl bromide

Nomenclature for the Example compounds was provided using ACD Name version 5.07 software (November 14, 2001) available from Advanced Chemistry Development, Inc. Some of the compounds and starting materials were named using standard IUPAC nomenclature.

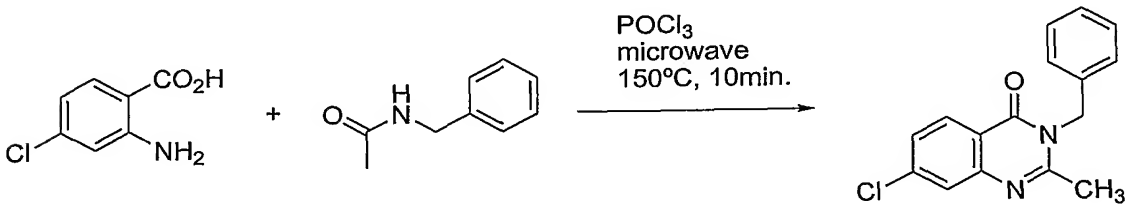
It should be understood that the organic compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure.

It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

Example 1

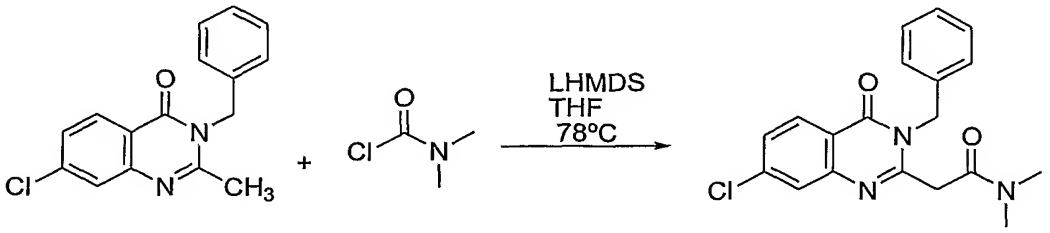
Synthesis of *N*-(3-aminopropyl)-*N*-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide

Step 1: 3-benzyl-7-chloro-2-methylquinazolin-4 (3*H*)-one.



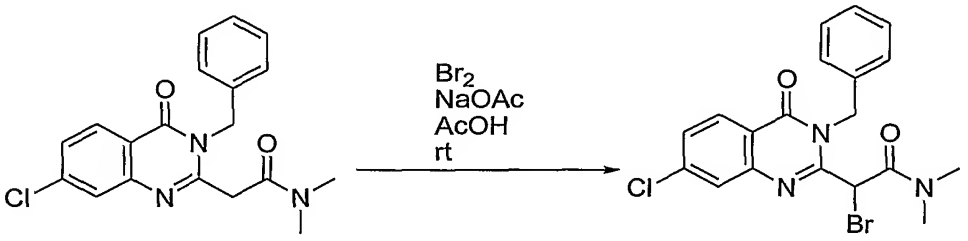
2-Amino-4-chlorobenzoic acid (250 mg, 1 eq.) and N-benzylacetamide (261 mg, 1.2 eq.) were dissolved in phosphorus oxychloride (2 ml). The reaction was placed in the microwave for 10 minutes at 150°C. The reaction was quenched by pouring the mixture into ice. The crude product was extracted into ethyl acetate. The ethyl acetate layer was washed with water, 10% aqueous sodium hydroxide, dried with magnesium sulfate, filtered, and concentrated to yield 3-benzyl-7-chloro-2-methylquinazolin-4 (3*H*)-one as an orange solid.

Step 2: 2-(3-benzyl-7-chloro-4-oxo-3, 4-dihydroquinazolin-2-yl)-*N*,*N*-dimethyl-acetamide.



3-Benzyl-7-chloro-2-methylquinazolin-4 (3*H*)-one (2 g, 1 eq.) was dissolved in tetrahydrofuran (20 ml). The solution was cooled to -78°C for 15 minutes. Lithium hexamethyl disilazide (LHMDS) was added slowly and the mixture was stirred at –78°C for 45 minutes. Dimethylcarbamyl chloride was added and the mixture was stirred at -78°C for 1 h. The reaction was allowed to warm to room temperature and stirred for 3 h. The solvent was evaporated and the resulting solid was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography to give 2-(3-benzyl-7-chloro-4-oxo-3, 4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide (1.2 g) as a solid.

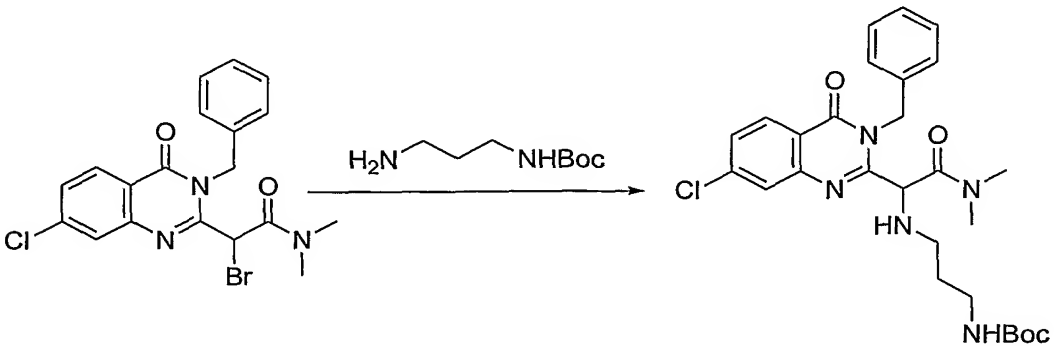
Step 3: 2-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-bromo-*N*,*N*-dimethylacetamide.



To a mixture 2-(3-benzyl-7-chloro-4-oxo-3, 4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide (1.1 g, 1 eq.) and sodium acetate (761 mg, 3 eq.) in acetic acid (15 ml), was added bromine (158 ul, 1 eq.) and the reaction was stirred at room temperature for 4 h. Water was added and the product extracted into ethyl acetate. The ethyl acetate layer was washed several times with water, saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to

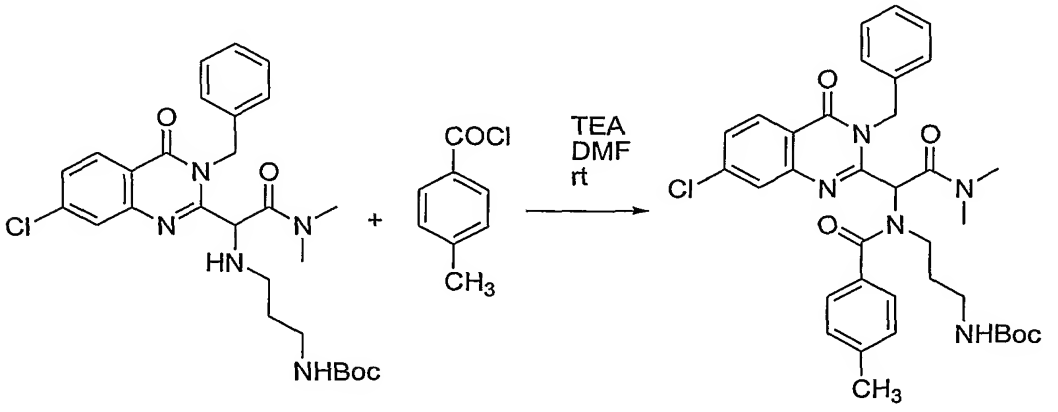
give 2-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-bromo-*N*,*N*-dimethylacetamide (1.44 g) as a yellow solid.

Step 4: *tert*-butyl 3-{[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]amino}propylcarbamate.



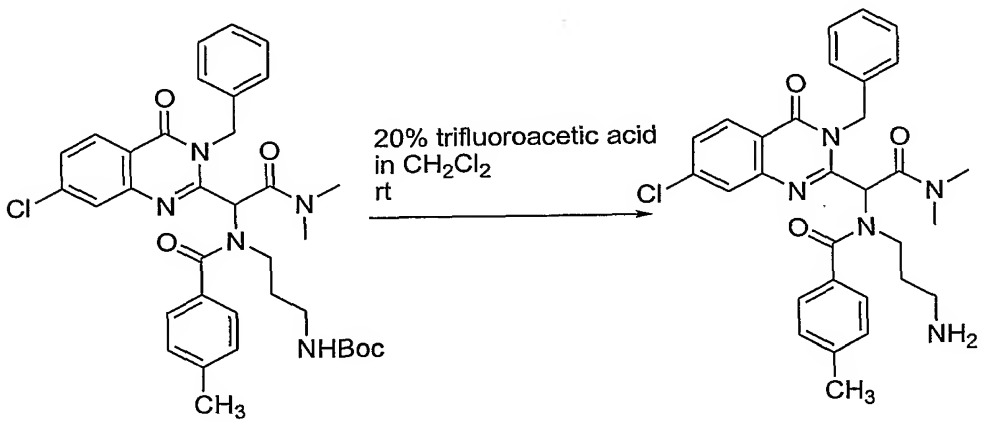
To a solution of 2-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-bromo-*N*,*N*-dimethylacetamide (1.4 g, 1 eq.) in of N,N-dimethylformamide (10 ml), was added N-Boc-1,3-diaminopropane (2.8 g, 5 eq.). The reaction was stirred at room temperature for 4 h and then heated to 40°C. The mixture was stirred at 40°C overnight. Water and ethyl acetate were added to the mixture. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography to give *tert*-butyl 3-{[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]amino}propylcarbamate (1 g) as a pale yellow solid.

Step 5: *tert*-butyl 3-[[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propylcarbamate.



To a solution of *tert*-butyl 3-{[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]amino}propylcarbamate (500 mg, 1 eq.) in methylene chloride (5 ml), was added 4-methyl benzoyl chloride (380 ul, 3 eq.) and triethylamine (660 ul, 5 eq.). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the crude product was dissolved in ethyl acetate. Ethyl acetate layer was washed with water, saturated sodium carbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and evaporated to yield crude *tert*-butyl 3-[[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propylcarbamate.

Step 6: *N*-(3-aminopropyl)-*N*-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide.

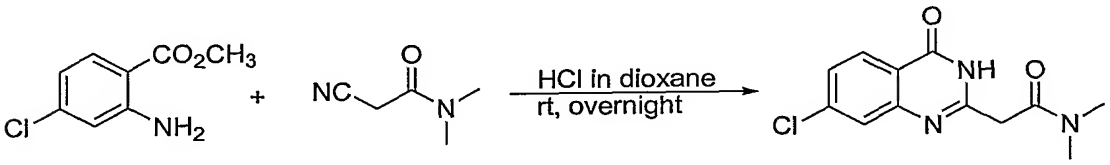


To a solution of *tert*-butyl 3-[[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propylcarbamate (500 mg), was added 20% solution of trifluoroacetic acid in methylene chloride at room temperature. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography to give *N*-(3-aminopropyl)-*N*-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide (336 mg) as a white solid.

Example 2

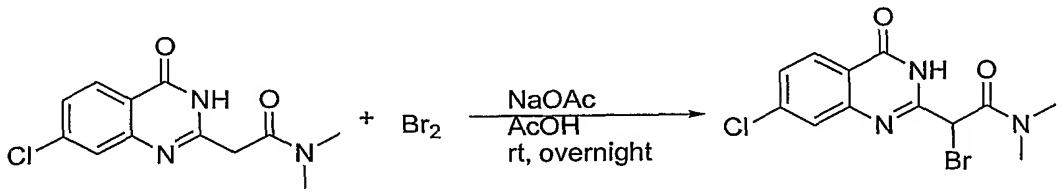
Synthesis of *N*-(3-aminopropyl)-*N*-[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide

Step 1: 2-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide.



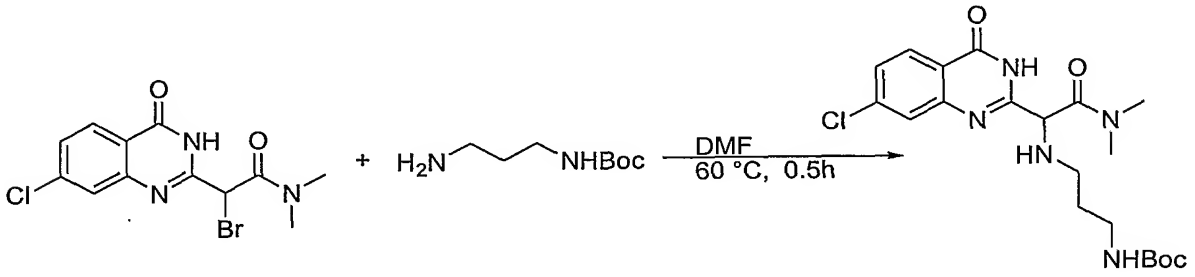
To a mixture of 2-amino-4-chloro methyl benzoate (5 g, 1 eq.) and N,N-dimethylamino acetamide (3.63 g, 1.2 eq.), was added a solution of 4M HCl in dioxane (40 ml). The reaction was stirred at room temperature overnight. Dioxane was removed at reduced pressure and the resulting solid residue was triturated with cold water. The aqueous solution was basified with 10% ammonium hydroxide. The precipitate was collected, washed with more cold water, washed with ether and dried to yield 2-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide 7.4 g (96 %) as a white solid.

Step 2: 2-bromo-2-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*,*N*-dimethyl-acetamide.



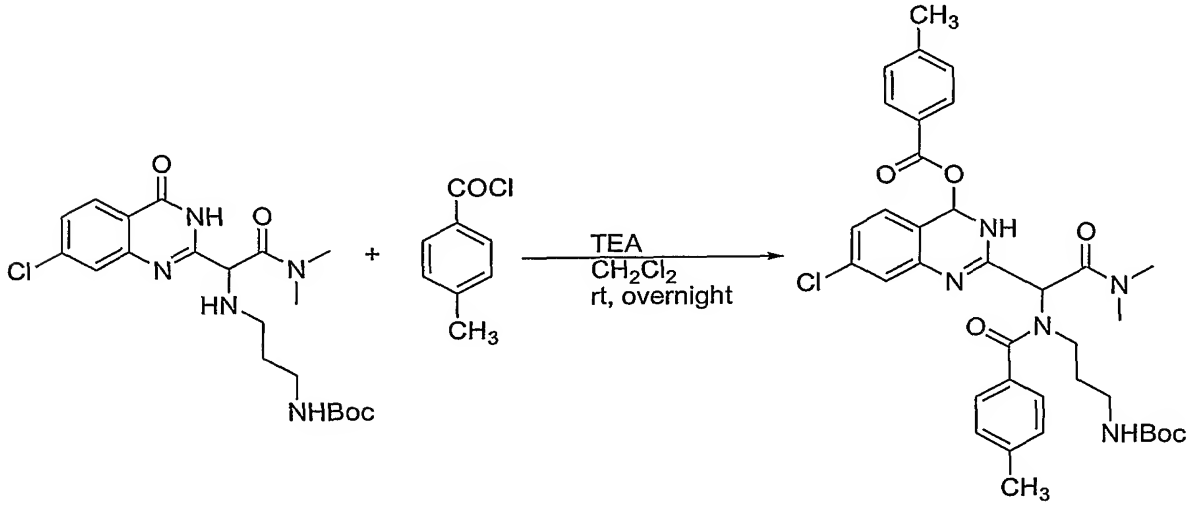
To a mixture of 2-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide and sodium acetate (930 mg, 3 eq.) in acetic acid (15 ml), was added bromine (190 ul, 1 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the product was extracted into ethyl acetate. The ethyl acetate layer was washed several times with water, saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give 2-bromo-2-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide (0.95 g) as a brown solid.

Step 3: *tert*-butyl 3-{[1-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]amino}propylcarbamate.



To a solution of 2-bromo-2-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*,*N*-dimethylacetamide (950 mg, 1 eq.) in N,N-dimethylformamide (10 ml), was added N-Boc-1,3-diaminopropane (2.4 g, 5 eq.). The reaction was stirred at 60 °C for 30 minutes. Water and ethyl acetate was added. Ethyl acetatelayer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated to give *tert*-butyl 3-{[1-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]amino}propylcarbamate (1.2 g) as a pale orange solid.

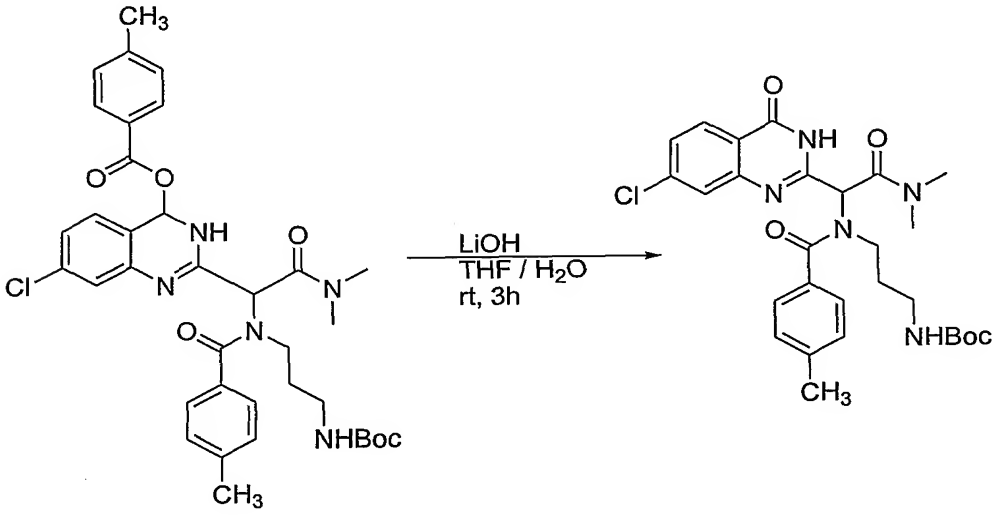
Step 4: 2-[1-[{3-[(*tert*-butoxycarbonyl)amino]propyl}(4-methylbenzoyl)amino]-2-(dimethylamino)-2-oxoethyl]-7-chloro-3,4-dihydroquinazolin-4-yl 4-methylbenzoate.



To a solution of *tert*-butyl 3-{[1-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]amino}propylcarbamate (1.2 g, 1 eq.) methylene chloride

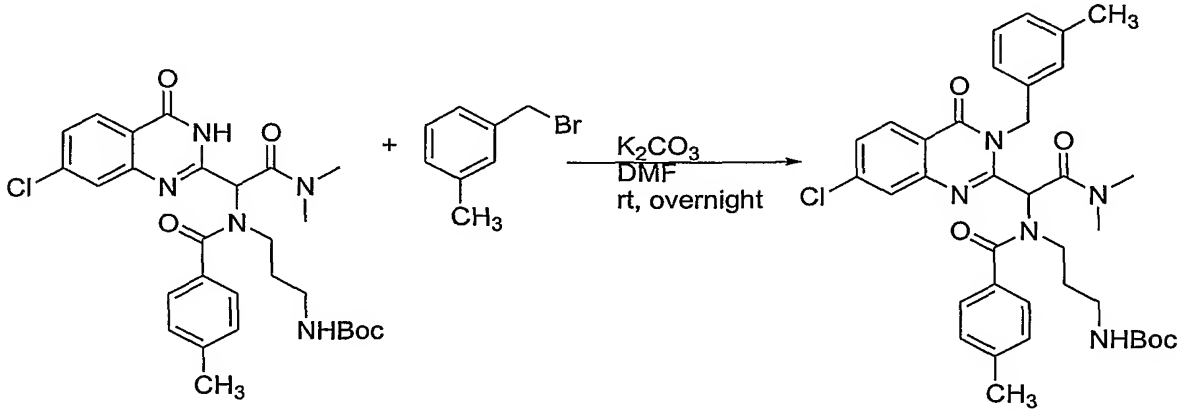
920 ml) at 0 °C, was added 4-methyl benzoyl chloride (1.1 ml, 3 eq.) and triethylamine (1.9 ml, 5 eq.). The reaction was allowed to warm up to room temperature and stirred at room temperature overnight. The solvent was evaporated and the crude product was dissolved in ethyl acetate. Ethyl acetate layer was washed with water, saturated sodium carbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and evaporated to yield 2-[1-[{3-[(*tert*-butoxycarbonyl)amino]propyl}(4-methylbenzoyl)amino]-2-(dimethylamino)-2-oxoethyl]-7-chloro-3,4-dihydroquinazolin-4-yl 4-methylbenzoate (2.3 g) as a brown oil.

Step 5: *tert*-butyl 3-[[1-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethyl-amino)-2-oxoethyl](4-methylbenzoyl)amino]propylcarbamate.



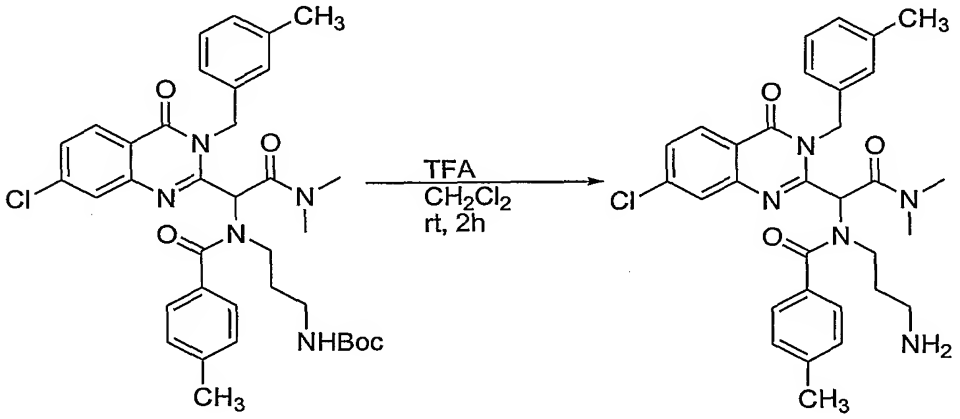
To a solution of 2-[1-[{3-[(*tert*-butoxycarbonyl)amino]propyl}(4-methylbenzoyl)amino]-2-(dimethylamino)-2-oxoethyl]-7-chloro-3,4-dihydroquinazolin-4-yl 4-methylbenzoate in a 1:1 mixture of tetrahydrofuran and water (20 ml), was added lithium hydroxide (284 mg, 2 eq.) at room temperature. The mixture was stirred at room temperature for 3 h. The reaction mixture was acidified with 1M of aqueous hydrogen chloride to pH 6 – 7 and later extracted into methylene chloride. The organic layer was washed with more water, dried over magnesium sulfate, filtered and concentrated. The product was purified by flash chromatography to give *tert*-butyl 3-[[1-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)-amino]-propylcarbamate (257 mg) as a yellow solid.

Step 6: *tert*-butyl 3-[[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydro-quinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propyl-carbamate.



To a solution of *tert*-butyl 3-[[1-(7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propylcarbamate (29 mg, 1 eq.) in dimethyl formamide (1 ml), was added 3-methylbenzyl bromide (8 µl, 1.2 eq.) and potassium carbonate (22 mg, 3 eq.). The reaction mixture was stirred at room temperature overnight. Water was added and the material was extracted into ethyl acetate. Ethyl acetate layer was washed with water, saturated sodium carbonate, saturated sodium chloride, dried over magnesium sulfate, filtered, and evaporated. The product was purified by flash chromatography to give *tert*-butyl 3-[[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propylcarbamate.

Step 7: *N*-(3-aminopropyl)-*N*-[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide.



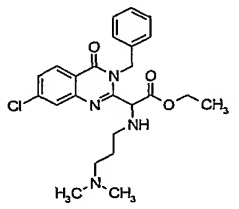
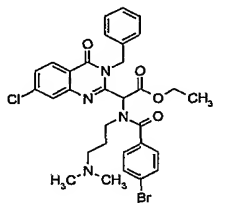
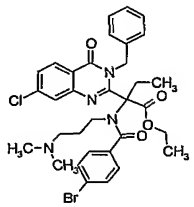
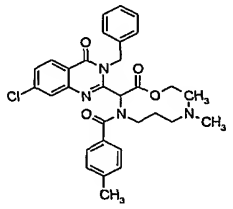
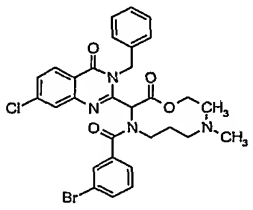
To a solution of *tert*-butyl 3-[[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl](4-methylbenzoyl)amino]propyl-carbamate, was added 20% solution of trifluoroacetic acid in methylene chloride at room temperature. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The crude product was purified by reverse phase HPLC to give *N*-(3-aminopropyl)-*N*-[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide (9 mg) as TFA salt.

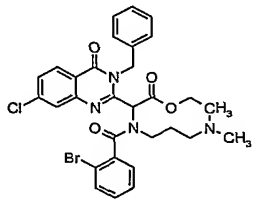
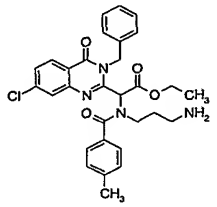
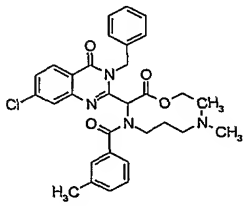
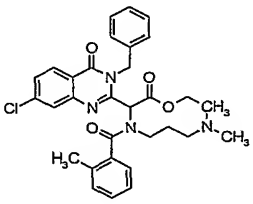
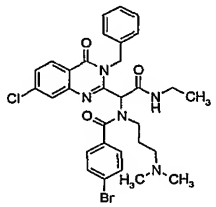
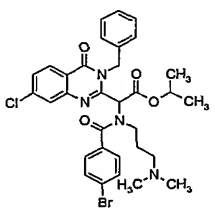
Example 3

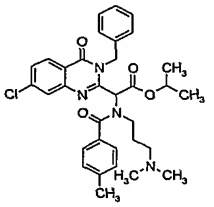
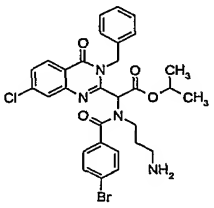
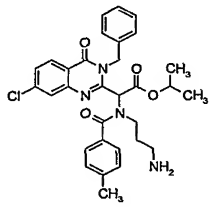
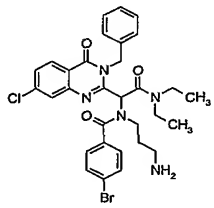
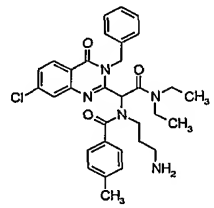
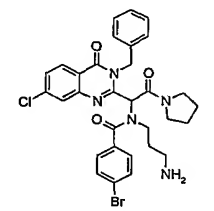
Representative Quinazolinone Compounds

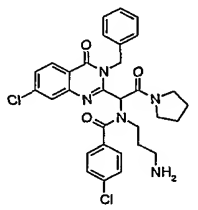
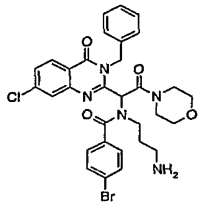
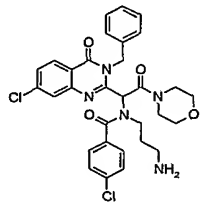
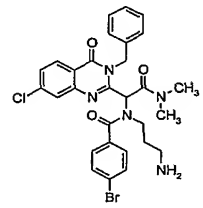
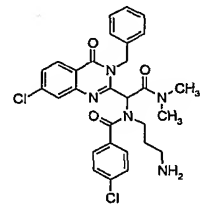
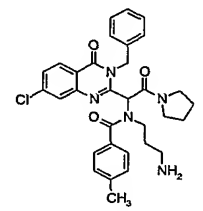
Representative quinazolinone compound compounds of the invention are shown in Table 1. In Table 1, MH+ refers to the molecular ion observed by mass spectrometry.

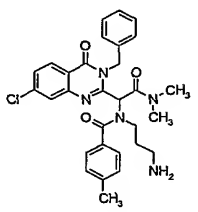
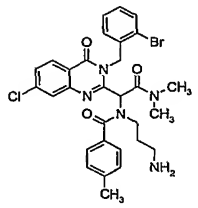
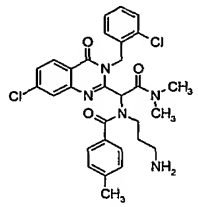
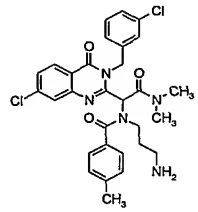
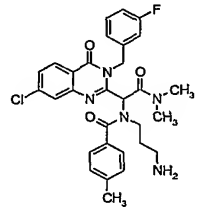
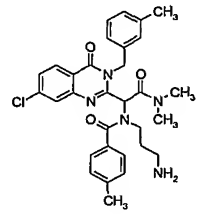
Table 1. Representative Quinazolinone Compounds.

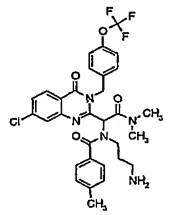
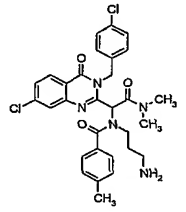
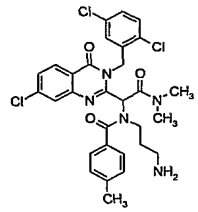
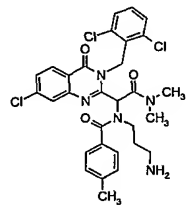
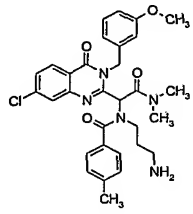
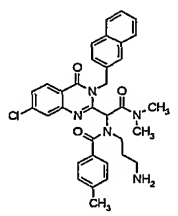
Compound	Structure	MH+	Name
1		458.0	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl){[3-(dimethylamino)propyl]amino}acetate
2		641.0	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl){(4-bromobenzoyl)[3-(dimethylamino)propyl]amino}acetate
3		669.0	ethyl 2-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-{(4-bromobenzoyl)[3-(dimethylamino)propyl]amino}butanoate
4		576.1	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)[[3-(dimethylamino)propyl](4-methylbenzoyl)amino]acetate
5		641.0	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl){(3-bromobenzoyl)[3-(dimethylamino)propyl]amino}acetate

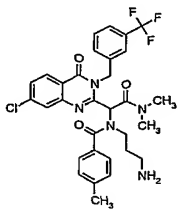
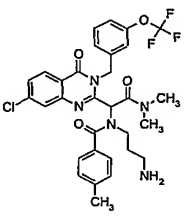
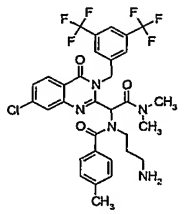
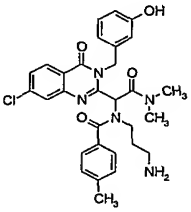
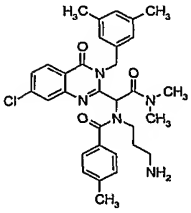
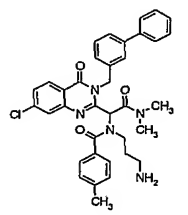
Compound	Structure	MH+	Name
6		641.0	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl){(2-bromobenzoyl)[3-(dimethylamino)propyl]amino}acetate
7		548.1	ethyl [(3-aminopropyl)(4-methylbenzoyl)amino](3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)acetate
8		576.1	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)[[3-(dimethylamino)propyl](3-methylbenzoyl)amino]acetate
9		576.1	ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)[[3-(dimethylamino)propyl](2-methylbenzoyl)amino]acetate
10		640.0	N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(ethylamino)-2-oxoethyl]-4-bromo-N-[3-(dimethylamino)propyl]benzamide
11		655.0	isopropyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl){(4-bromobenzoyl)[3-(dimethylamino)propyl]amino}acetate

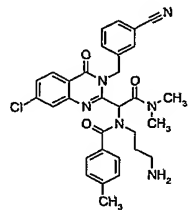
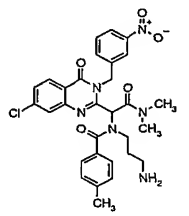
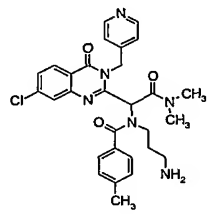
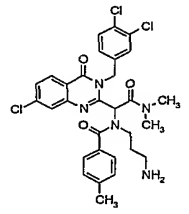
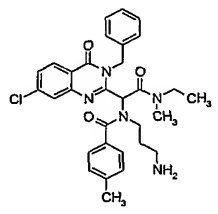
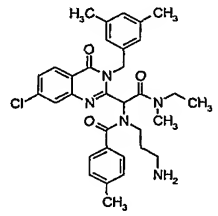
Compound	Structure	MH+	Name
12		590.1	isopropyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)[[3-(dimethylamino)propyl](4-methylbenzoyl)amino]acetate
13		626.9	isopropyl [(3-aminopropyl)(4-bromobenzoyl)amino](3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)acetate
14		562.1	isopropyl [(3-aminopropyl)(4-methylbenzoyl)amino](3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)acetate
15		640.0	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(diethylamino)-2-oxoethyl]-4-bromobenzamide
16		575.1	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(diethylamino)-2-oxoethyl]-4-methylbenzamide
17		638.0	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-oxo-2-pyrrolidin-1-ylethyl]-4-bromobenzamide

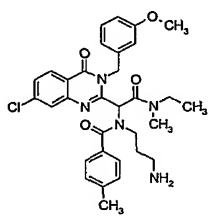
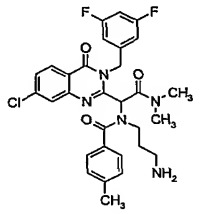
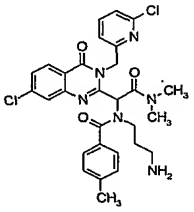
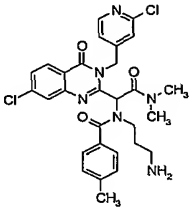
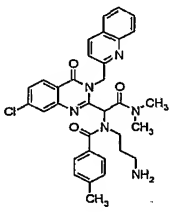
Compound	Structure	MH+	Name
18		593.5	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-oxo-2-pyrrolidin-1-ylethyl]-4-chlorobenzamide
19		654.0	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-morpholin-4-yl-2-oxoethyl]-4-bromobenzamide
20		609.5	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-morpholin-4-yl-2-oxoethyl]-4-chlorobenzamide
21		611.9	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-bromobenzamide
22		567.5	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-chlorobenzamide
23		573.1	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-oxo-2-pyrrolidin-1-ylethyl]-4-methylbenzamide

Compound	Structure	MH+	Name
24		547.1	N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
25		626.0	N-(3-aminopropyl)-N-[1-[3-(2-bromobenzyl)-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
26		581.5	N-(3-aminopropyl)-N-[1-[7-chloro-3-(2-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
27		581.5	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
28		581.5	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
29		565.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide

Compound	Structure	MH+	Name
30		631.1	N-(3-aminopropyl)-N-[1-{7-chloro-4-oxo-3-[4-(trifluoromethoxy)benzyl]-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
31		581.5	N-(3-aminopropyl)-N-[1-[7-chloro-3-(4-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
32		616.0	N-(3-aminopropyl)-N-[1-[7-chloro-3-(2,5-dichlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
33		616.0	N-(3-aminopropyl)-N-[1-[7-chloro-3-(2,6-dichlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
34		577.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
35		597.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(2-naphthylmethyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide

Compound	Structure	MH+	Name
36		615.1	N-(3-aminopropyl)-N-[1-{7-chloro-4-oxo-3-[3-(trifluoromethyl)benzyl]-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
37		631.1	N-(3-aminopropyl)-N-[1-{7-chloro-4-oxo-3-[3-(trifluoromethoxy)benzyl]-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
38		683.1	N-(3-aminopropyl)-N-[1-{3-[3,5-bis(trifluoromethyl)benzyl]-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
39		563.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-hydroxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
40		575.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3,5-dimethylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
41		623.2	N-(3-aminopropyl)-N-[1-[3-(1,1'-biphenyl-3-ylmethyl)-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide

Compound	Structure	MH+	Name
42		572.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-cyanobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
43		592.1	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-nitrobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
44		548.1	N-(3-aminopropyl)-N-[1-[7-chloro-4-oxo-3-(pyridin-4-ylmethyl)-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
45		616.0	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3,4-dichlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
46		561.1	N-(3-aminopropyl)-N-{1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide
47		589.1	N-(3-aminopropyl)-N-{1-[7-chloro-3-(3,5-dimethylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide

Compound	Structure	MH+	Name
48		591.1	N-(3-aminopropyl)-N-{1-[7-chloro-3-(3-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide
49		583.0	N-(3-aminopropyl)-N-[1-[7-chloro-3-(3,5-difluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
50		582.5	N-(3-aminopropyl)-N-[1-{7-chloro-3-[(6-chloropyridin-2-yl)methyl]-4-oxo-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
51		582.5	N-(3-aminopropyl)-N-[1-{7-chloro-3-[(2-chloropyridin-4-yl)methyl]-4-oxo-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide
52		598.1	N-(3-aminopropyl)-N-[1-[7-chloro-4-oxo-3-(quinolin-2-ylmethyl)-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide

Using the procedure described in Example 4, the above compounds were shown to have an KSP inhibitory activity at an IC_{50} of less than about 50 μM. Certain of the compounds have an IC_{50} of less than about 1 μM, and certain others of the compounds have an IC_{50} of less than about 100 nM.

Example 4

Assay for Determining KSP Activity

In this example, a representative in vitro assay for determining KSP activity is described.

Purified microtubules from bovine brain were purchased from Cytoskeleton Inc. The motor domain of human KSP (Eg5, KNSL1) was cloned and purified to a purity of greater than 95%. Biomol Green was purchased from Affinity Research Products Ltd.

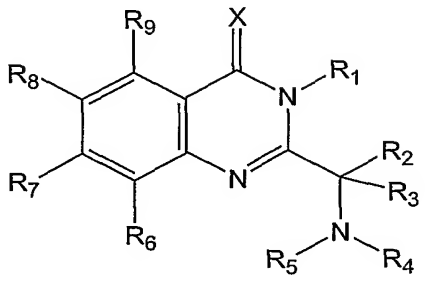
Microtubules and the KSP motor protein were diluted in assay buffer (20 mM Tris-HCl, pH 7.5, 1 mM $MgCl_2$, 10 mM DTT and 0.25 mg/ml BSA) to a concentration of 35 ug/ml for microtubules and 45 nM for KSP. The microtubule/KSP mixture was then pre-incubated at 37°C for 10 min to promote the binding of KSP to microtubules. ATP was also diluted to a concentration of 300 uM in the same assay buffer. To each well of the testing plate (384 well plate) containing 1.25 uL of compounds in DMSO or DMSO only, 25 uL of ATP solution. To start the reaction, 25 uL of microtubule/KSP solution was added to the ATP/compound mixture. The plates were incubated at room temperature for 1 hr. At the end of incubation period, 65 uL of Biomol Green was added to each well. The plates were incubated for 5-10 min and then the absorbance at 630 nm was determined. Biomol Green reagent is a malachite green based dye that detects the release of inorganic phosphate. Developed color signal was read using a Victor II reader. The concentration of each compound for 50% inhibition (IC_{50}) was calculated by nonlinear regression using either XLFit for Excel or Prism data analysis software by GraphPad Software Inc.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

CLAIMS:

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound having the formula:



or a stereoisomer, tautomer, pharmaceutically acceptable salt, or prodrug thereof, wherein

X is O or S;

R_1 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl,

(7) substituted or unsubstituted heterocyclyl,

(8) substituted or unsubstituted alkylsulfonyl, and

(9) substituted or unsubstituted arylsulfonyl;

R_2 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl, and

(4) substituted or unsubstituted alkynyl;

R_3 is selected from the group consisting of

(1) CO_2R_{10},

(2) COR_{10},

(3) $CONR_{11}R_{12}$,

(4) $S(O)_mR_{13}$, and

(5) $SO_2NR_{14}R_{15}$; or

R_2 and R_3 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic or heterocyclic ring;

with the proviso that when R_4 and R_5 are taken together to form a 5- to 12-membered heterocyclic ring, R_3 is $CONR_{11}R_{12}$ or R_2 and R_3 taken together with the carbon atom to which they are attached form a 3- to 7-membered carbocyclic or heterocyclic ring;

R_4 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl, and

(7) substituted or unsubstituted heterocyclyl;

R_5 is selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkoxy,

(4) substituted or unsubstituted aryl,

(5) substituted or unsubstituted heteroaryl,

(6) substituted or unsubstituted heterocyclyl,

(7) COR_{17},

(8) CO_2R_{18},

(9) $CONR_{19}R_{20}$, and

(10) SO_2R_{21}; or

R_4 and R_5 are taken together with the nitrogen atom to which they are attached form a heteroaryl or heterocyclyl ring, wherein the heteroaryl ring contains one or two ring heteroatoms, wherein the heterocyclyl ring contains one or two ring heteroatoms, and wherein the heteroaryl or heterocyclyl ring is optionally substituted with a halogen, alkyl, hydroxy, amino, cyano, alkylamino, dialkylamino, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, aryl, aryloxy, heteroaryl, arylalkyl, heterocycle, aminocarbonyl, carbonylamino,

alkylcarbonyl, alkylcarboxy, alkylaminocarbonyl, alkylcarbonylamino, carbocycle, or heteroarylalkyl group; with the proviso that when R_4 and R_5 taken together with the nitrogen atom to which they are attached form a 5-membered heterocyclic ring, the heterocyclic ring is not a 2,4-dioxo-3-oxazolidinyl ring, a 2,5-dioxo-1-imidazolidinyl ring, or a 2,4,5-trioxo-1-imidazolidinyl ring;

R_6, R_7, R_8, and R_9 are independently selected from the group consisting of

(1) hydrogen,
(2) halogen,
(3) hydroxy,
(4) nitro,
(5) amino,
(6) cyano,
(7) alkoxy,
(8) alkylthio,
(9) methylenedioxy,
(10) haloalkoxy,
(11) CO_2R_{10},
(12) COR_{10},
(13) OR_{10},
(14) $CONR_{11}R_{12}$,
(15) substituted or unsubstituted alkyl,
(16) substituted or unsubstituted aryl,
(17) substituted or unsubstituted heteroaryl,
(18) substituted or unsubstituted alkylamino,
(19) substituted or unsubstituted dialkylamino,
(20) substituted or unsubstituted alkylsulfonyl,
(21) substituted or unsubstituted arylsulfonyl,
(22) substituted or unsubstituted alkylcarboxy,
(23) substituted or unsubstituted carboxamido,
(24) substituted or unsubstituted carboxyamino,
(25) substituted or unsubstituted aminocarboxy,
(26) substituted or unsubstituted aminocarbonyl, and
(27) substituted or unsubstituted alkylsulfonamido;

R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of

(1) hydrogen,

(2) substituted or unsubstituted alkyl,

(3) substituted or unsubstituted alkenyl,

(4) substituted or unsubstituted alkynyl,

(5) substituted or unsubstituted aryl,

(6) substituted or unsubstituted heteroaryl, and

(7) substituted or unsubstituted heterocyclyl; or

R_{11} and R_{12}, R_{14} and R_{15}, or R_{19} and R_{20} taken together form a 3- to 7-membered carbocyclic or heterocyclic ring; and

m = 0, 1, or 2.

2. A compound of Claim 1, wherein substituted alkyl comprises arylalkyl, heteroarylalkyl, heterocyclyalkyl, aminoalkyl, alkylaminoalkyl, dialkyaminoalkyl, or sulfonamidoalkyl.

3. A compound of Claim 1, wherein X is O.

4. A compound of Claim 1, wherein R_1 is substituted or unsubstituted arylalkyl.

5. A compound of Claim 4, wherein R_1 is benzyl.

6. A compound of Claim 4, wherein R_1 is substituted benzyl.

7. A compound of Claim 6, wherein R_1 is a halo-substituted benzyl.

8. A compound of Claim 7, wherein R_1 is 3-chlorobenzyl.

9. A compound of Claim 7, wherein R_1 is 3-fluorobenzyl.

10. A compound of Claim 7, wherein R_1 is 3-methoxybenzyl.

11. A compound of Claim 7, wherein R_1 is 3-trifluoromethylbenzyl.

12. A compound of Claim 7, wherein R_1 is 3-trifluoromethoxybenzyl.

13. A compound of Claim 6, wherein R_1 is 3,5-dimethylbenzyl.

14. A compound of Claim 1, wherein R_1 is 2-naphthylmethyl.

15. A compound of Claim 1, wherein R_2 is hydrogen and R_3 is CO_2R_{10}.

16. A compound of Claim 15, wherein R_{10} is alkyl.

17. A compound of Claim 1, wherein R_2 is hydrogen and R_3 is $CONR_{11}R_{12}$.

18. A compound of Claim 17, wherein R_{11} and R_{12} are alkyl.

19. A compound of Claim 18, wherein R_{11} and R_{12} are methyl.

20. A compound of Claim 17, wherein R_{11} and R_{12} taken together with the nitrogen atom to which they are attached from a 3- to 7-membered heterocyclic ring.

21. A compound of Claim 1, wherein R_4 is amino-substituted alkyl.

22. A compound of Claim 21, wherein R_4 is 3-aminopropyl.

23. A compound of Claim 1, wherein R_5 is hydrogen, alkyl, aryl, or COR_{17}.

24. A compound of Claim 23, wherein R_5 is COR_{17}.

25. A compound of Claim 24, wherein R_{17} is aryl, arylalkyl, alkyl-substituted aryl, or halogen-substituted aryl.

26. A compound of Claim 25, wherein aryl is phenyl

27. A compound of Claim 1, wherein R_6, R_8, and R_9 are hydrogen.

28. A compound of Claim 1, wherein R_7 is a halogen.

29. A compound of Claim 1 selected from the group consisting of:

ethyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl){(4-bromobenzoyl)[3-(dimethylamino)propyl]amino}acetate;

ethyl [(3-aminopropyl)(4-methylbenzoyl)amino](3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)acetate;

isopropyl (3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)[[3-(dimethylamino)propyl](4-methylbenzoyl)amino]acetate;

isopropyl [(3-aminopropyl)(4-bromobenzoyl)amino](3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)acetate;

isopropyl [(3-aminopropyl)(4-methylbenzoyl)amino](3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)acetate;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(diethylamino)-2-oxoethyl]-4-bromobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(diethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-oxo-2-pyrrolidin-1-ylethyl]-4-bromobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-oxo-2-pyrrolidin-1-ylethyl]-4-chlorobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-morpholin-4-yl-2-oxoethyl]-4-bromobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-morpholin-4-yl-2-oxoethyl]-4-chlorobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-bromobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-chlorobenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-oxo-2-pyrrolidin-1-ylethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-methylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-{7-chloro-4-oxo-3-[4-(trifluoromethoxy)benzyl]-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(4-chlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(2-naphthylmethyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-{7-chloro-4-oxo-3-[3-(trifluoromethyl)benzyl]-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-{7-chloro-4-oxo-3-[3-(trifluoromethoxy)benzyl]-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-hydroxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3,5-dimethylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[3-(1,1'-biphenyl-3-ylmethyl)-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-cyanobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3-nitrobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3,4-dichlorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-{1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide;

N-(3-aminopropyl)-N-{1-[7-chloro-3-(3,5-dimethylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide;

N-(3-aminopropyl)-N-{1-[7-chloro-3-(3,5-dimethylbenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide;

N-(3-aminopropyl)-N-{1-[7-chloro-3-(3-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-[ethyl(methyl)amino]-2-oxoethyl}-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-[7-chloro-3-(3,5-difluorobenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-{7-chloro-3-[(6-chloropyridin-2-yl)methyl]-4-oxo-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide;

N-(3-aminopropyl)-N-[1-{7-chloro-3-[(2-chloropyridin-4-yl)methyl]-4-oxo-3,4-dihydroquinazolin-2-yl}-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide; and

N-(3-aminopropyl)-N-[1-[7-chloro-4-oxo-3-(quinolin-2-ylmethyl)-3,4-dihydroquinazolin-2-yl]-2-(dimethylamino)-2-oxoethyl]-4-methylbenzamide.

30. A composition, comprising a pharmaceutically acceptable carrier and an amount of a compound of Claim 1 effective to inhibit KSP activity in a human or animal subject when administered thereto.

31. The composition of Claim 30 further comprising at least one additional agent for the treatment of cancer.

32. The composition of Claim 31, wherein the at least one additional agent for the treatment of cancer is selected from irinotecan, topotecan, gemcitabine, gleevec, herceptin, 5-fluorouracil, leucovorin, carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, and trastuzumab.

33. A method for treating a condition by modulation of KSP protein activity comprising administering to a human or animal subject in need of such treatment an effective amount of a compound of Claim 1.

34. The method of Claim 33, wherein the compound has an IC50 value of less than about 50 μM in a cell proliferation assay.

35. The method of Claim 33, wherein the condition is cancer.

36. A method for inhibiting KSP activity in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of Claim 1 effective to inhibit KSP activity the human or animal subject.

37. A method for treating a cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of Claim 1 effective to inhibit KSP activity the human or animal subject.

38. The method of Claim 37 further comprising administering to the human or animal subject at least one additional agent for the treatment of cancer.

39. The method of Claim 38, wherein the at least one additional agent for the treatment of cancer is selected from irinotecan, topotecan, gemcitabine, gleevec, herceptin, 5-fluorouracil, leucovorin, carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, and trastuzumab.

40. A compound of Claim 1 for use in the treatment of cancer.

41. Use of a compound of Claim 1 in the manufacture of a medicament for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/039448

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/90 C07D401/06 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/30768 A (CYTOKINETICS, INC; FINER, JEFFREY, T; BERGNES, GUSTAVE; FENG, BAINIAN;) 3 May 2001 (2001-05-03) cited in the application claims 1,2	1-14, 21-28, 30-41
Y		15-20,29
X	WO 01/98278 A (CYTOKINETICS, INC; FINER, JEFFREY, T; BERGNES, GUSTAV; FENG, BAINIAN;) 27 December 2001 (2001-12-27) cited in the application claims 1,2	1-14, 21-28, 30-41
Y		15-20,29
Y	WO 03/050064 A (MERCK & CO., INC; FRALEY, MARK, E; HARTMAN, GEORGE, D; HOFFMAN, WILLIA) 19 June 2003 (2003-06-19) cited in the application claims 1,15,30	15-20,29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 2005	16/02/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/039448

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 33-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/039448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0130768 A	03-05-2001	AU 774748 B2	08-07-2004
		AU 1439801 A	08-05-2001
		BR 0015110 A	02-07-2002
		CA 2388646 A1	03-05-2001
		CN 1413198 T	23-04-2003
		CZ 20021428 A3	13-11-2002
		EP 1226129 A1	31-07-2002
		HU 0203430 A2	28-05-2003
		JP 2003512461 T	02-04-2003
		JP 2003048881 A	21-02-2003
		MX PA02004162 A	20-08-2003
		NO 20021907 A	07-06-2002
		NZ 518480 A	27-02-2004
		PL 354891 A1	22-03-2004
		WO 0130768 A1	03-05-2001
		US 6545004 B1	08-04-2003
		US 6562831 B1	13-05-2003
		US 6630479 B1	07-10-2003
		US 6831085 B1	14-12-2004
		US 2004254203 A1	16-12-2004
		ZA 200202930 A	28-10-2002
		AU 5927001 A	02-01-2002
		BR 0111898 A	13-05-2003
		CA 2413426 A1	27-12-2001
		CN 1437585 T	20-08-2003
		CZ 20024178 A3	14-05-2003
		EP 1296959 A1	02-04-2003
		HU 0301201 A2	29-12-2003
		JP 2004501140 T	15-01-2004
		MX PA02012627 A	25-09-2003
		NO 20026172 A	20-02-2003
		NZ 523233 A	29-10-2004
		PL 358412 A1	09-08-2004
		WO 0198278 A1	27-12-2001
		US 2004023996 A1	05-02-2004
		ZA 200210133 A	17-06-2003
WO 0198278 A	27-12-2001	US 6545004 B1	08-04-2003
		AU 774748 B2	08-07-2004
		AU 1439801 A	08-05-2001
		AU 5927001 A	02-01-2002
		BR 0015110 A	02-07-2002
		BR 0111898 A	13-05-2003
		CA 2388646 A1	03-05-2001
		CA 2413426 A1	27-12-2001
		CN 1413198 T	23-04-2003
		CN 1437585 T	20-08-2003
		CZ 20021428 A3	13-11-2002
		CZ 20024178 A3	14-05-2003
		EP 1226129 A1	31-07-2002
		EP 1296959 A1	02-04-2003
		HU 0203430 A2	28-05-2003
		HU 0301201 A2	29-12-2003
		JP 2003512461 T	02-04-2003
		JP 2003048881 A	21-02-2003
		JP 2004501140 T	15-01-2004
		MX PA02004162 A	20-08-2003
		MX PA02012627 A	25-09-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/039448

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0198278 A		NO	20021907 A	07-06-2002
		NO	20026172 A	20-02-2003
		NZ	518480 A	27-02-2004
		NZ	523233 A	29-10-2004
		PL	354891 A1	22-03-2004
		PL	358412 A1	09-08-2004
		WO	0130768 A1	03-05-2001
		WO	0198278 A1	27-12-2001
		US	2004023996 A1	05-02-2004
		US	6562831 B1	13-05-2003
		US	6630479 B1	07-10-2003
		US	6831085 B1	14-12-2004
		US	2004254203 A1	16-12-2004
		ZA	200210133 A	17-06-2003
WO 03050064 A	19-06-2003	AU	2002357053 A1	23-06-2003
		CA	2467722 A1	19-06-2003
		EP	1463733 A2	06-10-2004
		WO	03050064 A2	19-06-2003